IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Beka SOLOMON

Application No. 09/441,140
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PREVENTION OF PROTEIN AGGREGATION

Examiner: K. Ballard
Art Unit: 1649

APPEAL BRIEF

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REAL PARTY IN INTEREST

The present reissue application, as well as the underlying patent, is owned by Ramot at Tel-Aviv University, Ltd. The co-exclusive licensees of the present application are Pfizer Inc., New York, NY, and Janssen Alzheimer Immunotherapy, Dublin, Ireland, a subsidiary of Johnson & Johnson, New Brunswick NJ.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF CLAIMS

Claims 177 and 210-228 are pending in the present application and all are subject to the present appeal. Claims 1-176 and 178-209 have been cancelled.

STATUS OF AMENDMENTS

Applicants' amendment of May 10, 2010, is the only amendment filed in this case after the final rejection of December 10, 2009. By the Advisory Action of June 11, 2010, the examiner stated that the amendment of May 10, 2010, would be entered for the purpose of appeal.

SUMMARY OF CLAIMED SUBJECT MATTER

The present invention is based on the discovery that antibodies can be found that can be used therapeutically to dissolve β-amyloid plaque or prevent formation of β-amyloid plaque in Alzheimer's patients. See, for example, column 6, lines 7-15 and lines 23-26. Before the present invention, this was not known.

The only independent claims in this case are claims 210, 212, 214, 215, 218, 219, 222, 224, 225 and 228. No means plus function or step plus function as permitted by 35 U.S.C. §112, sixth paragraph, are present in any of these claims.

Claim 210 is directed to a therapeutic composition comprising a pharmaceutical formulation. The specification describes pharmaceutical formulations in the paragraph beginning at column 9, line 21. The pharmaceutical formulation comprises a pharmaceutically acceptable carrier (see column 9, line 26) and either a genetically engineered antibody or a fragment thereof. The use of a genetically engineered antibody is supported, for example, in the sentence beginning at column 10, line 1, the first sentence of column 6, and the sentence beginning at column 9, line 45. The use of an antibody fragment is supported, for example, in the sentence beginning at column 9, line 45.

Both the genetically engineered antibody and the fragment thereof must bind β-amyloid and either inhibit aggregation of β-amyloid or maintain the solubility of soluble

β-amyloid to an extent at least as great as that obtainable with antibody AMY-33. That the antibody is an anti-β-amyloid antibody is supported by the sentence beginning at column 5, line 51. That the antibody binds β-amyloid is supported in the specification at column 3, lines 45-47, column 5, lines 30-32, column 6, lines 7-14, column 6, lines 21-26, and column 16, lines 5-6.

The concept of use of an antibody that inhibits aggregation or that maintains the solubility of β-amyloid to an extent at least as great as that obtainable with antibody AMY-33 is also supported by the present specification. For example, reference is made to column 6, lines 21-26, where it states:

> In the preferred embodiment the human monoclonal antibody that binds to an aggregating protein and which prevents aggregation is utilized. In a further preferred embodiment the monoclonal antibody is an anti-β-amyloid and is designated AMY-33 which recognizes amino acids 1-28 of β-amyloid.

Thus, the generic idea of using any antibody that prevents aggregation is presented, and the specific idea of using antibody AMY-33 as a preferred embodiment is also presented. As the genus of an antibody that inhibits any amount of aggregation and the species of an antibody that inhibits the same amount of aggregation as AMY-33 are both supported, the concept of use of an antibody within the range of the amount

of inhibition achieved by AMY-33 and up is also supported. Note also the present specification at column 16, lines 15-21, where it states:

> On the basis of applicants findings regarding other antigen-antibody systems studies …, the formation of the immunocomplexes with selected, highly specific monoclonal antibodies, should provide a general and convenient method to prevent aggregation of the proteins …. [Emphasis added]

Thus, it is clear that the present invention is directed to the use of "selected, highly specific monoclonal antibodies." An example of highly specific monoclonal antibody given is AMY-33. This further supports the use of any selected highly specific monoclonal antibody which inhibits aggregation at least to the extent of AMY-33. The issue of support for this term will be discussed further in the argument section of this Brief.

Claim 210 further provides that the genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that both (i) binds β-amyloid and inhibits aggregation of β-amyloid or maintains the solubility of soluble β-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and (ii) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of β-amyloid.

The concept that the genetically engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody is supported at column 10, lines 1-3, of the present specification where it states:

> The present invention uses genetically-engineered antibodies obtained from such selected antibodies ….

That the genetically-engineered antibodies are obtained by genetically engineering the DNA encoding the selected monoclonal antibodies is implicit or inherent in the above-quoted portion of the present specification.

Support for the antibody properties recited in (i) is the same as that discussed above with respect to the properties of the genetically engineered antibody. As for (ii), support is found at column 6, lines 23-27, column 15, lines 35-38, and column 15, lines 43-46.

Finally, claim 210 further provides that the antibody or fragment is not conjugated with a detectable moiety. This language is supported at column 11, at the paragraph beginning on line 52, where it states that the monoclonal antibody of the invention "can be bound to a solid support substrate or conjugated with a detectable moiety." It further states:

> The detectable moieties contemplated with the present invention can include, but are not limited to, fluorescent, metallic, enzymatic and radioactive markers ….

In view of the disclosure that the present application may include such markers, it also supports the concept that the antibodies exclude such markers. In other words, this is an option that the specification indicates can be present or not and the present claims specify the antibodies without that option.

Independent claim 212 differs from claim 210 in that, instead of reciting "a genetically engineered antibody" as part of the pharmaceutical formulation, it recites "a human monoclonal antibody." It also omits the characterization of the genetically engineered antibody that appears in claim 210. Support for "human monoclonal antibody" is found at column 6, lines 21-23, and column 7, lines 7-12. Support for the remaining language of claim 212 is the same as discussed above for claim 210.

Claim 214 is drawn to a method of making a therapeutic composition comprising a pharmaceutically acceptable carrier and a genetically-engineered antibody. The latter is described in the same language as in claim 210. Claim 214 is directed to the method that must inherently be used to produce the composition of claim 210. As discussed above, the specification at column 10, lines 1-3, clearly supports the concept of genetically engineered antibodies obtained from selected antibodies. Process claim 214 merely puts into process format the steps that must inherently be used to obtain and formulate such genetically engineered

antibodies. All of the other terms used in claim 214 are found in claim 210 and are supported for the same reasons as already explained for claim 210.

Independent claim 215 is identical to claim 210 except that the recitation of the properties of the monoclonal antibody in part (ii) of the first "wherein" clause provides that the antibody "recognizes an epitope within residues 1-28 of beta-amyloid," rather than the language in claim 210 that the antibody "is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid." The recitation about recognizing an epitope within residues 1-28 of β-amyloid is supported at column 5, lines 30-33, in conjunction with the disclosure at column 6, lines 23-27 and column 15, lines 35-38, and column 15, lines 43-46.

Independent claim 218 is identical to claim 214 except that the recitation of "recognizes an epitope within residues 1-28 of beta-amyloid" is used instead of the "obtainable" language used in claim 214. Support for this difference has already been explained with respect to independent claim 215.

Independent claims 219, 222, 224, 225 and 228 are identical to corresponding claims 210, 212, 214, 215 and 218 except for one difference, which is the same difference in each of these claims. Whereas the first set of claims (210, 212, 214, 215 and 218) use the language, "inhibits aggregation of human beta-amyloid or maintains the solubility of soluble

human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33," the corresponding claims 219, 222, 224, 225 and 228 substitute the language, "disaggregates an aggregate of β-amyloid." Support for the requirement of the antibody or fragment as being effective to disaggregate an aggregate of β-amyloid may be found, for example, in the paragraph beginning column 5, line 23, and the sentence beginning at column 5, line 40.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 177 and 210-218 have been rejected under the written description requirement of 35 USC 112, first paragraph, on the basis of alleged new matter. The examiner takes the position that there is no support in the specification as originally filed for anti-β-amyloid antibodies that inhibit aggregation of β-amyloid to a particular specified degree, much less one that is described in terms of meeting or exceeding the ability of the antibody AMY-33 to inhibit β-amyloid.

Claims 177 and 210-218 have also been rejected under the written description requirement of 35 USC 112, first paragraph, on the basis of the breadth of the genus. The examiner takes the position that the recitation of an antibody capable of inhibiting aggregation of soluble β-amyloid in a subject "to an extent at least as great as that obtainable with antibody AMY-33" does not meet the written description provision of 35 U.S.C. 112, first paragraph, because there is insufficient guidance and direction of the genus of antibodies broadly encompassed by the claimed invention.

Claims 177, 210-213 and 215-217 have been rejected under 35 USC 103(a) as being unpatentable over Bickel et al. (*Bioconjugate Chem,* 5(2):119-125 (1994)) (hereinafter referred to as Bickel), as evidenced by Solomon (*Expert Opin Biol Ther,* 2(8):907-917 (2002)) (hereinafter referred to as Solomon 2002), and in view of EP 0613 007 A2 to Becker et al.

(published 08/31/1994) (hereinafter referred to as Becker) and US Patent No. 4,946,778 to Ladner et al. (issued August 7, 1990) (hereinafter referred to as Ladner).

Claims 177, 210-213, 215-217, 219-223 and 225-227 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Walker et al. (*J Neuropathol Exp Neurol*, 53(4):377-383 (1994 Jul)) (hereinafter referred to as Walker), as evidenced by Hanan and Solomon (*Amyloid: Int J Exp Clin Invest*, 3:130-133 (1996)) (hereinafter referred to as Hanan) and Bacskai et al. (*Nat Med* 7(3):369-372 (2001)) (hereinafter referred to a Bacskai), in view of Becker.

ARGUMENTS

Claims 177 and 210-218 are Fully Supported by the Disclosure and Contain No Prohibited New Matter.

For the purpose of the present new matter rejection, all of claims 177 and 210-218 are considered to stand or fall together.

The examiner states that there is no support in the specification as originally filed for anti-β-amyloid antibodies that inhibit aggregation of β-amyloid to a particular specified degree, much less one that is described in terms of meeting or exceeding the ability of the antibody AMY-33 to inhibit β-amyloid aggregation. The examiner states that there is neither verbatim support for this claim language nor does it flow naturally from the disclosure as originally filed. The examiner states that the specification does not describe any assay that could be used to test the anti-aggregating abilities of candidate antibodies and compare them directly to that AMY-33. The examiner states that the disclosure of a preferred embodiment usually implies the highest or best embodiment achievable or known to applicants at the time of filing. This rejection is respectfully traversed.

First of all, the examiner is incorrect in stating that the specification does not contain an assay for comparing the anti-aggregating abilities of candidate antibodies. Figures 7A and 7B show the result of an assay that compares

the anti-aggregating properties AMY-33 and 6F/3D. Particularly, the second bar of section 1 of these two figures quantitatively shows that AMY-33 has a much greater ability to prevent aggregation than 6F/3D. This same assay may be used to compare any two antibodies.

The written description guidelines set forth in MPEP 2163 state at section I B:

> While there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure.

Here, the newly added claim language is supported in the specification through implicit or inherent disclosure. The concept of the use of any antibody that binds to Aβ and prevents aggregation is present in the present specification as filed, for example, at column 16, line 21-26. Furthermore AMY-33 was indicated as being a preferred embodiment in that same passage. While the examiner states that it must be presumed that AMY-33 is as good as it gets, one of ordinary skill in the art reading the present specification would not believe that. It can be seen that the specification describes testing on Aβ of only two antibodies having the required epitope specificity. One of those two was much better than the other one and was thus indicated as being preferred (between the two). However, no one of ordinary skill in the art would have considered that, once one raises and tests other antibodies for these properties, other antibodies having

properties even better than those shown in the assay of Figure 7A might be found.

Accordingly, the present specification contains the generic concept of all antibodies that bind β-amyloid and inhibit aggregation or cause disaggregation of β-amyloid and are either obtainable by using a particular fragment of Aβ as an immunogen or recognizing a particular epitope of Aβ. This includes the entire range of anti-aggregating activity. Additionally, the specification teaches the specific anti-aggregating activity shown in Figure 7A for AMY-33. Thus, there is implicit or inherent support for that range beginning at the activity of AMY-33 shown in Figure 7A and higher. In this regard, note MPEP 2163.05 III, relating to range limitations, where it states:

> With respect to changing numerical range limitations, the analysis must take into account which ranges one skilled in the art would consider inherently supported by the discussion in the original disclosure. In the decision in *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976), the ranges described in the original specification included a range of "25%-60%" and specific examples of "36%" and "50%". A … limitation to "between 35% and 60%" did meet the description requirement.

By that logic, the range from that amount of activity possessed by AMY-33 (see Figure 7A(1)) and higher, is inherently supported by the disclosure of the full range of activities that include an activity barely above negligible to

the highest amount possible, in combination with the specific example with the number shown in Figure 7A(1). Reversal of the examiner and withdrawal of this rejection are therefore respectfully urged.

Claims 177 and 210-218 are Fully Supported by the Present Disclosure, Which Shows Possession by the Inventor for the Entire Scope of the Claimed Genus

For the purpose of the present new matter rejection, all of claims 177 and 210-218 are considered to stand or fall together.

The examiner states that the claims broadly recite a therapeutic composition comprising a genetically engineered antibody or fragment thereof that inhibits aggregation of β-amyloid or maintains the solubility of β-amyloid to an extent at least as great as that obtainable with antibody AMY-33 and is obtainable using a peptide consisting of residues 1-28 of β-amyloid as an immunogen. The examiner states that the language about inhibiting aggregation to an extent at least as great as that obtained with antibody AMY-33 would imply the use and possession not only of antibodies having anti-aggregating abilities the same as that of the mAb AMY-33 but also of antibodies having anti-aggregating properties exceeding that AMY-33. Therefore, the claims are drawn to a genus of genetically engineered antibodies having a degree of functional activity equal to or greater than the functional activity of AMY-33. The examiner states that the

specification does not provide guidance or support for a class of antibodies determined to meet or exceed the functional ability of the antibody AMY-33 to inhibit β-amyloid aggregation. The examiner states that applicant has only demonstrated one species within the genus, which species uses AMY-33, and this does not constitute a representative number of species such that one would recognize that applicant was in possession of the invention as broadly claimed. The examiner states that the skilled artisan cannot envision the detailed chemical structure of the encompassed genetically engineered antibodies. This rejection is respectfully traversed.

Contrary to the examiner's statement, the present specification does provide support or guidance for classifying antibodies based upon a particular level of functional activity. Example 2 in the present specification shows that monoclonal antibody AMY-33 prevents self-aggregation in the presence or absence of heparan sulfate and/or metal ions. On the other hand, monoclonal antibody 6F/3D was ineffective without the presence of Zn^{2+} and even then was only partially effective. Clearly, therefore, the specification does provide classification based on a level of functional activity. Negligible activity, such as that obtained with mAb 6F/3D was clearly distinguished from the good prevention of aggregation shown by mAb AMY-33. These antibodies were clearly classified based on a particular level of functional activity.

Previously, the claims read on all levels of functional activity, thus reading on the genus that includes AMY-33 - and all other antibodies raised against the claimed immunogen or recognizing the claimed sequence - which bind to β-amyloid and which inhibit aggregation or induce disaggregation. When the examiner took the position that the claims previously read on antibodies with only minimal activity, the claims were amended to recite that the activity must be at least as great as that of AMY-33. The claims now only read on those antibodies that have the functional activity of AMY-33 or better. Just as applicant was in possession of the entire genus prior to the amendment limiting to the activity of AMY-33 or better, so applicant is in possession of the subgenus which eliminates all those antibodies that have an activity less than that obtainable with AMY-33.

The Written Description Training Materials, Revision 1, March 25, 2008, available on the PTO website (http://www.uspto.gov/web/menu/written.pdf) is particularly relevant. As stated in *Ex parte Scott*, Appeal 2008-004077, (Bd. Pat. App. & Int. 2010), available at http://des.uspto.gov/Foia/ReterivePdf?system=BPAI&flNm=fd2008004077-01-05-2010-3, states at slip opinion page 21:

> The Written Description Guidelines, and by extension their accompanying Training Materials, do not have the force of law but they do reflect the USPTO's usual application of the law to similar facts. To

> the extent that they do not conflict with the statute or binding case law, therefore, they are entitled to consideration.

These training materials, at pages 45-46, have a specific example relating to antibodies against a single protein. This is Example 13, which discusses written description support for a claim drawn to "an isolated antibody capable of binding to antigen X." In this example, the specification disclosed antigen X and discussed antibodies which specifically bind to antigen X but it had no working or detailed prophetic example of an antibody that binds to antigen X. The training materials analyze this situation, at pages 45 and 46, as follows:

> The specification does not describe an actual reduction to practice of an antibody that binds to antigen X by reference to a deposit (e.g., deposit of a hybridoma) or by describing an antibody in structural terms sufficient to show possession. The specification also does not describe the complete structure of an antibody capable of binding antigen X in detailed drawings or through a structural chemical formula. The specification does not describe a partial structure of the claimed antibody. The specification does not describe any physical or chemical properties of the claimed antibody (e.g., molecular weight, association constant).
>
> The specification does not disclose a correlation between the function of binding to antigen X and the structure of the claimed antibody. Finally, the specification does not describe a method of making an antibody that binds antigen X.

> However, the level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against a well-characterized antigen was conventional.
>
> Antibodies were known to be of five general types; each of the five types had been characterized as having substantial common structural, chemical and biological features.
>
> The antigen-specific variable regions of antibodies vary.
>
> It does not appear that persons of skill in the art consider knowledge of the amino acid sequence of the variable regions critical for purposes of assessing possession of an antibody.
>
> Considering the facts, including the routine art-recognized method of making antigen-specific antibodies, the adequate description of antigen X, the well-defined structural characteristics for the classes, subclasses and isotypes of antibody, the functional characteristics of antibody binding, and the fact that antibody technology was well developed and mature, one of skill in the art would have recognized that the disclosure of the adequately described antigen X put the applicant in possession of antibodies which bind to antigen X.

Accordingly, the example concluded that the specification satisfied the written description requirement with respect to the full scope of claim 1. These training materials were formally acknowledged and given judicial notice by the Federal

Circuit in *Enzo Biochem Inc. v. GenProbe Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002).

The present claims are supported in the manner required by the written description requirement of 35 USC 112 for reasons similar to those set forth in the above training materials example. The present specification includes one example of the claimed antibody, which is more than the specification had in the above example. The examiner makes much of the fact that the present claims are "genus" claims that encompass a genus of antibody molecules differing in structure and epitope specificity. But the same is true for the claim being analyzed in Example 13 of the training materials. The antibody could be specific to any epitope on the protein designated as antigen X and each of the antibodies would differ in structure. Obviously, this is not a substantive difference between the present situation and the claim of Example 13. The fact remains that the level of skill and knowledge in the art of antibodies at the time of filing (note that the art relied on for this fact in the training materials was dated in 1976) was such that the production of antibodies against a well-characterized antigen was conventional. The knowledge of the amino acid sequence of the variable regions is not critical for purposes of assessing possession of the antibody. The art is well aware of the well-defined structural characteristics for the classes, subclasses and isotypes of antibody, the functional

characteristics of antibody binding, and the fact that antibody technology was well developed and mature.

The present claims differ from the claim of Example 13 in that it is narrower than the recitation of antibodies in Example 13. The present claims do not cover every antibody that is specific to an epitope within 1-28 of Aβ, but requires another screen of the selected antibodies to select only those that inhibit β-amyloid aggregation or maintains the solubility of soluble β-amyloid, and then a step to compare the degree of inhibition activity or solubility maintenance activity with that of known and available antibody AMY-33. The fact that the claim is narrower than what is permitted by the training materials does not make it lose written description support. The specification discloses that such selection and comparison is necessary. An example of one antibody within the scope of the claims is given. Antibody technology is still well developed and mature and the further screens are routine. Thus, the subgenus of the present claims is supported for the same reason that the genus of Example 13 is supported.

Accordingly, in view of the disclosure of the antigen to which the antibody is specific, as well as the disclosure of certain additional screens which must be run in order to make sure that the antibody obtained has all of the claimed properties, and further in view of the well known structure-function relationship of antibody to antigen, one of

ordinary skill in the art would understand that the inventor was in possession of the claimed genus.

Claims 177, 210-213 and 215-217 Are Not Made Obvious by Any Combination of Bickel, Solomon 2002, Becker or Ladner

For the purpose of the present obviousness rejection, all of claims 177, 210-213 and 215-217 are considered to stand or fall together.

A. It Would Not be Obvious to Genetically Engineer Antibody AMY-33.

The examiner states that Bickel teaches monoclonal antibody AMY-33 and its use as an *in vivo* diagnostic. The examiner relies upon the present specification and the post-filing date publication, Solomon 2002, as evidence that AMY-33 will inherently have the property of inhibiting β-amyloid deposition. The examiner states that Bickel suggests the use of monoclonal antibodies for therapeutic use in the last sentence thereof. The examiner cites Becker and Ladner for the desirability of genetically engineering an antibody intended for therapeutic use to make it into a single chain antibody. The examiner states that applicant's previous arguments are not persuasive because, while diagnostic use of AMY-33 antibody is one utility suggested by Bickel, Bickel also suggests that humanized monoclonal antibodies or antibodies having reduced immunogenicity could be used therapeutically. This rejection is respectfully traversed.

All of claims 177, 210-213 and 215-217 have a "wherein" clause specifying that the antibody or fragment "is not conjugated with a detectable moiety." The only specific utility taught by Bickel is a diagnostic utility. For a diagnostic utility, the antibody must be conjugated to a detectable moiety, such as a fluorescent, metallic, enzymatic or radioactive marker. Bickel does not suggest or enable any use for which such a detectable moiety would not be necessary. It is the examiner's position, however, that Bickel does indeed teach a therapeutic utility in the last sentence thereof.

The last paragraph of Bickel begins with the statement that the "^{111}In-labeled cationized AMY-33 has been developed as a tool for radioimmunoimaging of cerebral amyloid deposits using SPECT technology." The paragraph then goes on to state that other antibodies may be evaluated as diagnostic tools. The paragraph then continues with a discussion of the generalities of antibodies used for *in vivo* diagnostic tools, stating that it is desirable to diminish their immunogenicity. The paragraph then concludes with the sentence:

> Therefore, the "humanization" of murine monoclonal antibodies prior to mAb cationization may facilitate the use of these proteins as neurodiagnostic or therapeutic agents in humans (49).

This statement is applicable to any antibody that one wishes to use as neurodiagnostic or therapeutic agents in humans.

One of ordinary skill in the art reading the entirety of Bickel would never believe that this last sentence, which is really a generic statement applicable to all antibodies that can be used either as neurodiagnostic or a therapeutic agent in humans, contains a suggestion that AMY-33 has any properties that would make it useful as a therapeutic agent. This sentence is not a suggestion that the specific antibody AMY-33 is useful as a therapeutic agent in humans. If it were such a suggestion, this would be a *non-sequitur* as the rest of Bickel gives no suggestion that there might be any possible therapeutic use for AMY-33. Certainly, there is no enabling disclosure in Bickel for any kind of therapeutic use for AMY-33.

The only disclosed *in vivo* use for this antibody is as a diagnostic after it has been cationized and labeled with a radiodetectable marker. Thus, the examiner's basis for this rejection, i.e., that one of ordinary skill in the art would find it obvious to use AMY-33 as a therapeutic, simply fails as there is absolutely nothing in Bickel which would suggest this. The reference to therapeutic agents in humans in the last sentence of Bickel clearly is a generic statement relating to any antibody that may be used as a neurodiagnostic or a therapeutic agent. Bickel would not be considered by one of ordinary skill in the art as a disclosure that AMY-33, without a detectable moiety, might be used as a therapeutic

agent, particularly in the absence of any suggestion of why or how it could be said as such.

No utility whatsoever is taught or suggested by Bickel for AMY-33 without a detectable moiety. Thus, one of ordinary skill in the art would not be motivated by Solomon 2002, Becker or Ladner to genetically engineer AMY-33 so as to make a pharmaceutical formulation with a genetically engineered AMY-33 that does not have a detectable marker attached to the antibody. Accordingly, reversal of the examiner and withdrawal of this rejection are respectfully urged.

B. The Use of a Post-Filing Date Publication to Establish Obviousness is Error

The presently rejected claims all require that the pharmaceutical formulation of the claimed therapeutic composition include a genetically-engineered antibody, or a human monoclonal antibody, or a fragment thereof, that not only binds β-amyloid, but also "inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33." The examiner cites the post-filing date publication Solomon 2002 as evidence that AMY-33 will inherently have the property of inhibiting β-amyloid deposition. However, this allegedly inherent characteristic of AMY-33 was not known at the time of the effective filing date of the present application. Obviousness cannot be predicated on what is

unknown. See *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993), where it states:

> "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Spormann*, 53 C.C.P.A. 1375, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966). Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection. See *In re Newell*, 891 F.2d 899, 901, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989).

The facts in this case differ from those involved in *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009). In *Kubin*, the claims were directed to the cDNA encoding a known protein. One of the claims included the limitation, "wherein the polypeptide binds CD48." That claim recitation left no choices; it merely stated an inherent property of the known protein that was encoded by the claimed cDNA. The court held that the prior art did not need to disclose that limitation. In the present case, the claims are not directed to a composition that only reads on the use of a single identified antibody. In other words, the claims are not directed to a genetically engineered AMY-33. They are directed to a genetically engineered antibody that has been selected for certain properties. That AMY-33 had such properties was unknown at the time of the effective date of the present application, even though this property may have been inherent. Obviousness cannot be predicated on what was unknown. Thus, the reliance on applicant's own specification and a post-

filing date publication to establish obviousness was improper. For this reason as well, reversal of the examiner and withdrawal of this rejection are respectfully urged.

Claims 177, 210-213, 215-217, 219-223 and 225-227 Are Not Made Obvious by Any Combination of Walker, Hanan, Bacskai or Becker.

For the purpose of the present obviousness rejection, all of claims 177, 210-213, 215-217 are considered to stand or fall together. However, claims 219-223 and 225-227 are separately patentable and, while they stand or fall together, must be considered independently of the other claims. Sections A, B and C below are applicable to all of the claims. Section D is particularly directed to claims 219-223 and 225-227.

A. It Would Not be Obvious to Genetically Engineer Antibody 10D5.

The examiner states that Walker suggests that antibody 10D5 may be employed to deliver therapeutic agents directly to β-amyloid in the brain. The examiner relies on post-filing date publications, Hanan and Bacskai, to evidence the fact that antibody 10D5 inherently has the properties of inhibiting aggregation and causing disaggregation of β-amyloid as are presently claimed. The examiner states that Walker, in light of the other evidence, establishes that the antibody thereof has all of the claimed limitations except that it is not genetically engineered, such as into a single chain

antibody. The examiner states that Becker discloses that anti-β-amyloid antibodies useful for the treatment of Alzheimer's disease may be genetically engineered. The examiner concludes that it would have been obvious at the time the invention was made to genetically engineer the 10D5 monoclonal antibody to create a less immunogenic antibody molecule, such as a single chain antibody, for use in therapeutic applications as taught by both Walker and Becker. This part of the rejection is respectfully traversed.

Just as with Bickel, Walker does not teach any therapeutic use for antibody 10D5. While Walker suggests that there may be therapeutic utility for an antibody that can bind to β-amyloid in the brain in order to deliver therapeutic agents that could prevent or reverse β-amyloid deposition in the brains of patients with cerebral vascular amyloidosis or Alzheimer's disease, Walker does not teach that any such therapeutic agents exist.

Furthermore, even if such therapeutic agents existed, Walker does not teach that antibody 10D5, when bound to such therapeutic agents, would still bind to β-amyloid *in vivo*. This general disclosure of Walker is only a recognition that, if such therapeutic agents against amyloid deposition were ever discovered in the future, then antibody 10D5 might be of interest as a research tool to try to deliver those therapeutic agents to the brain. But Walker certainly provides no present motivation for one of ordinary skill in

the art at the time the present invention was made to humanize antibody 10D5 or to make it into a single chain antibody. Becker only suggests that this would be obvious to do with an antibody known to have some type of therapeutic or other *in vivo* utility. Such was not known for antibody 10D5 at the time the present invention was made.

The only utility for antibody 10D5 taught by Walker is a diagnostic utility in combination with imaging technology, such as PET or SPECT, to diagnose β-amyloidosis in living subjects. However, PET and SPECT require labeled antibodies and the present claims exclude labeled antibodies. It is true that the experiments of Walker do not use labeled antibodies, but this is only because they were able to remove the brains of the monkeys studied and then label the antibodies with a secondary labeled antibody using PAP and DAB. This is obviously not possible for diagnostic use of such antibodies in humans.

Accordingly, no combination of Walker with Becker teaches or suggests any motivation to genetically engineer the antibody of Walker. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

B. The Use of a Post-Filing Date Publication to Establish Obviousness is Error

The presently rejected claims all require that the pharmaceutical formulation of the claimed therapeutic composition include a genetically-engineered antibody, or a

human monoclonal antibody, or a fragment thereof, that not only binds β-amyloid, but also either "inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33," (claims 177, 210-213 and 215-217) or "disaggregates an aggregate of β-amyloid" (claims 219-223 and 225-227). The examiner cites the post-filing date publications Hanan and Bacskai as evidence that antibody 10D5 will inherently have the property of inhibiting β-amyloid deposition and disaggregating an aggregate of β-amyloid. However, this allegedly inherent characteristic of 10D5 was not known at the time of the effective filing date of the present application. Obviousness cannot be predicated on what is unknown. See *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993), where it states:

> "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Spormann*, 53 C.C.P.A. 1375, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966). Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection. See *In re Newell*, 891 F.2d 899, 901, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989).

The facts in this case differ from those involved in *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009). In *Kubin*, the claims were directed to the cDNA encoding a known protein. One of the claims included the limitation, "wherein the polypeptide binds CD48." That claim recitation left no

choices; it merely stated an inherent property of the known protein that was encoded by the claimed cDNA. The court held that the prior art did not need to disclose that limitation. In the present case, the claims are not directed to a composition that only reads on the use of a single identified antibody. In other words, the claims are not directed to a genetically engineered 10D5. They are directed to a genetically engineered antibody that has been selected for certain properties. That 10D5 had such properties was unknown at the time of the effective date of the present application, even though this property may have been inherent. Obviousness cannot be predicated on what was unknown. Thus, the reliance on post-filing date publications to establish obviousness was improper. For this reason as well, reversal of the examiner and withdrawal of this rejection are respectfully urged.

C. It Would Not Have Been Obvious at the Time the Invention was Made that Antibody 10D5 Possessed the Claimed Properties

Those of ordinary skill in the art aware of the literature that has been published on the subject of amyloid-binding antibodies to date are well aware that not all antibodies raised against β-amyloid will necessarily have the property of inhibiting aggregation of β-amyloid or maintaining the solubility of soluble β-amyloid to an extent at least as great as that obtainable with antibody AMY-33 or the property of disaggregating an aggregate of β-amyloid. First of all,

the present specification clearly states that the antibodies having the desired properties have to be selected (see, for example, at column 5, lines 23-24 and column 6, line 9). The example shows that while AMY-33, which is raised against the 1-28 fragment of Aβ, inhibits β-amyloid aggregation, monoclonal antibody 6F/3D, recognizing an epitope located between the residues 8-17 of the β-amyloid, does not work.

Furthermore, attached hereto is a Table (this Table is the same as that attached to applicant's amendment of September 23, 2009) listing, to applicant's knowledge, all of the antibodies that have been tested in the literature for either prevention of aggregation of β-amyloid *in vitro*, disaggregation of β-amyloid *in vitro* or *ex vivo*, or disaggregation of β-amyloid *in vivo*. It can be seen that while AMY-33 and eight other antibodies that bind to an epitope between residues 1 and 7 of β-amyloid have shown positive results, one antibody having an epitope of 1-7 had negative results, one that had an epitope of 4-10 had negative results and all of the antibodies having epitopes between 10 and 28 (six other antibodies) showed negative results. Furthermore, three antibodies directed to an epitope between 33 and 42 showed negative results. The publications from which these results were culled are all of record in the case.

These results prove that it cannot have been expected at the time of the present invention that all antibodies that recognize an epitope between 1-28 of Aβ will

prevent aggregation of β-amyloid or will cause aggregated β-amyloid to disaggregate. The Solomon 2002 reference does not teach to the contrary as it states that antibodies must be directed to a "strategic" position on the antigen molecule. See page 908, second column, at the end of the first partial paragraph, where it states:

> For such an active role, mAbs require a high binding constant to the 'strategic' positions on the antigen molecule.

See also the first full paragraph on page 910 where this publication states:

> Disaggregation, as well as the prevention of amyloid formation, was found to be dependent on the location of the epitopes on the Aβ and on the binding characteristics of the respective antibodies.
>
> Using the phage-peptide libraries, composed of filamentous phage displaying random combinatorial peptides, the author defined the EFRH residues located at positions 3-6 of the N-terminal AβP as the epitope of anti-aggregating antibodies 6C6 and 10D5 within AβP. … The mAb 2H3, which did not affect Aβ formation, despite the fact that it binds to the N-terminal of AβP, highlights the importance of this specific sequence region on the behavior of the whole AβP molecule.

Thus, this publication confirms that antibodies raised against the first 28 amino acids of β-amyloid do not necessarily have anti-aggregating properties, including solubilization of existing β-amyloid aggregates and inhibition of β-amyloid

aggregation. A very specific epitope within 1-28 is required, as evidenced by the fact that mAb 2H3 does not affect Aβ formation. It should be noted that mAb 2H3 appears on the attached Table.

In order to avoid the unintended reading of the claims as to include antibodies with only a very small amount of inhibiting activity, which includes negligible amounts of inhibition, the present claims have been amended to recite that the antibody must inhibit aggregation of β-amyloid or maintain the solubility of soluble β-amyloid "to an extent at least as great as that obtainable with the antibody AMY-33." All of the antibodies in the Table that are indicated as being negative in inhibition of aggregation of β-amyloid, have substantially less inhibition than is achieved by AMY-33. Thus, the present claims do not read on the negligible amounts of inhibition that may be shown for such antibodies. Thus, the present claims now only read on antibodies that have a substantial amount of inhibiting activity.

Accordingly, while antibody 10D5 does inherently have the properties required for an antibody of the present invention, this fact was unknown and would not have been obvious at the time the present invention was made. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown. Not only were these properties unknown, but they were unobvious and unpredictable. The evidence discussed herein establishes that this is not

simply a property that accompanies any antibody raised against β-amyloid, or raised against the 1-28 fragment of β-amyloid. Antibodies raised against such a fragment or against the full protein must be screened for the inhibiting or disaggregating properties required by the claims. It would not have been obvious at the time the invention was made that antibody 10D5 would have such properties. Such properties yield results that, by definition, rebut any case of *prima facie* obviousness. The examiner says that it would be obvious to make genetically engineered antibody 10D5 without a diagnostic marker thereon just to carry therapeutic agents to amyloid plaque. However, such antibodies unexpectedly have the property of inhibiting aggregation of β-amyloid and causing disaggregation of β-amyloid plaque. These unexpected properties rebut any case of *prima facie* obviousness (although, for the reasons discussed above, applicant does not concede that such a case of *prima facie* obviousness has been established). For these reasons as well, the examiner should be reversed and this rejection withdrawn.

D. The Compositions of Claims 219-223 and 225-227 Have Additional Particularly Unexpected Properties

Claims 219-228 all require that the antibody disaggregate an aggregated β-amyloid. This activity is even more selective than inhibition of amyloid aggregation. It can be seen from the attached Table that antibodies that cause disaggregation are even rarer than antibodies that inhibit

aggregation. Accordingly, these claims should be considered separately and are independently free of this rejection.

CONCLUSION

All of the present claims are in full compliance with the written description requirement of 35 USC 112 and none are rendered obvious by any of the references of record. For all of the reasons herein, reversal of the examiner and allowance of all of the claims now present in the case are earnestly solicited.

Respectfully submitted,

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TABLE

Antibody	Immunogen	Epitope	Disaggregate *In vivo*	Disaggregate *In vitro* or *Ex vivo*	Prevention of Aggregation *In Vitro*
AMY-33	1-28[6]	?			+[2, 6]
6C6	1-28[5]	3-7[5]		+[5, 7]	+[2, 7, 8, 10]
10D5	1-28[5]	3-6[11]	+[1, 3]	+[5, 11]	+[2, 8, 10]
3D6	1-5[4]	1-5[11]	+[3]	+[5, 11]	
12B4	1-42[5]	3-7[5]		+[5]	
2C1	1-42[5]	3-7[5]		+[5]	
12A11	1-42[5]	3-7[5]		+[5]	
3A3	1-42[5]	3-7[5]		+[5]	
22C8		3-7[11]		+[11]	
2H3	1-12[4]	1-7[10]			–[2, 8, 10]
6E10		5-10[11]		–[11]	
14A8		4-10[11]		–[11]	
18G11		10-18		–[11]	
1C2	13-28[7]	13-28[7]		–[7]	–[2, 7, 8]
16C11	23-42[5]	23-42[5]	–[3]	–[5, 11]	
266	13-28[4]	16-24[11]	–[9]	–[5, 11]	–[8]
22D12	13-28[5]	18-21[11]		–[5, 11]	
6F/3D	8-17[6]				–[6]
21F12	33-42[4]	33-42[5]	–[3]	–[5, 11]	
14C2		33-40[7]		–[7]	–[7]
2G3	33-40[4]			–[11]	

[1] Bacskai et al., "Imaging of Amyloid-β Deposits in Brains of Living Mice Permits Direct Observation of Clearance of Plaques with Immunotherapy", *Nature Medicine*, 7:369-372 (2001)
[2] Hanan et al., "Inhibitory Effect of Monoclonal Antibodies on Alzheimer's β-Amyloid Peptide Aggregation", *Amyloid: Int. J. Exp. Clin. Invest.*, 3:130-133 (1996)
[3] Bard et al., "Peripherally Administered Antibodies Against Amyloid β-Peptide Enter the Central Nervous System and Reduce Pathology in a Mouse Model of Alzheimer Disease", *Nature Medicine*, 6:916-919 (2000)
[4] Johnson-Wood et al., "Amyloid Precursor Protein Processing and $A\beta_{42}$ Deposition in a Transgenic Mouse Model of Alzheimer Disease", *Proc. Natl. Acad. Sci. USA*, 94:1550-1555 (1997)
[5] Bard et al., "Epitope and Isotype Specificities of Antibodies to β-Amyloid Peptide for Protection Against Alzheimer's Disease-like Neuropathology", *Proc. Natl. Acad. Sci. USA*, 100:2023-2028 (2003)
[6] Solomon et al., "Monoclonal Antibodies Inhibit *in vitro* Fibrillar Aggregation of the Alzheimer β-Amyloid Peptide", *Proc. Natl. Acad. Sci. USA*, 93:452-455 (1996)
[7] Solomon et al., "Disaggregation of Alzheimer β-Amyloid by Site-Directed mAb", *Proc. Natl. Acad. Sci. USA*, 94:4109-4112 (1997)
[8] Solomon et al., "The Amino Terminus of the β-Amyloid Peptide Contains an Essential Epitope for Maintaining its Solubility", in *Progress in Alzheimer's and Parkinson's Diseases*, Fisher et al., ed., Plenum Press, New York, 205-211 (1998)
[9] DeMattos et al., "Peripheral Anti-Aβ Antibody Alters CNS and Plasma Aβ Clearance and Decreases Brain Aβ Burden in a Mouse Model of Alzheimer's Disease", *Proc. Natl. Acad. Sci. USA*, 98:88-50-8855 (2001)
[10] Frenkel et al., "High Affinity Binding of Monoclonal Antibodies to the Sequential Epitope EFRH of β-Amyloid Peptide is Essential for Modulation of Fibrillar Aggregation", *Journal of Neuroimmunology*, 95:136-142 (1999)
[11] Schenk., US 6,761,888 – Table 16 (col 63)

CLAIMS APPENDIX

This listing of claims includes all of the claims involved in the appeal.

Listing of Claims:

177. The therapeutic composition of claim 210 or 211, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

210. A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or

(b) a fragment of the genetically-engineered antibody of (a) that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-

amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid; and

wherein said antibody or fragment is not conjugated with a detectable moiety.

211. The therapeutic composition of claim 210, wherein said genetically-engineered antibody of (2)(a) binds human beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or said fragment of (2)(b) binds human beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that binds human beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33 and said monoclonal antibody is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of human beta-amyloid.

212. A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a human monoclonal antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or

(b) a fragment of the human monoclonal antibody of (a) that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33,

wherein said human monoclonal antibody is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid.

213. The therapeutic composition of claim 212, wherein said human monoclonal antibody of (2)(a) binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or said fragment of (2)(b) binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and wherein said human monoclonal antibody of (a) is obtainable using an

immunogen consisting of a peptide consisting of residues 1-28 of human beta-amyloid.

214. A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or (b) a fragment of the genetically-engineered antibody of (a), which fragment binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, said method comprising:

selecting a monoclonal antibody that

(i) binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of

soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or a fragment of a genetically engineered antibody, which fragment binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

215. A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or

(b) a fragment of the genetically-engineered antibody of (a) that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid, and

wherein said antibody or fragment is not conjugated with a detectable moiety.

216. The therapeutic composition of claim 215, wherein said genetically-engineered antibody of (2)(a) binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or said fragment of (2)(b) binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33 and said monoclonal antibody recognizes an epitope within residues 1-28 of human beta-amyloid.

217. The therapeutic composition of claim 215 or 216, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

218. A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or (b) a fragment of the genetically-engineered antibody of (a), which fragment binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, said method comprising:

selecting a monoclonal antibody that

(i) binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of

soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or a fragment of a genetically engineered antibody, which fragment binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

219. A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or

(b) a fragment of the genetically-engineered antibody of (a) that binds beta-amyloid and disaggregates an aggregate of β-amyloid,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) binds beta-amyloid and disaggregates an aggregate of β-amyloid and

(ii) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid, and

wherein said antibody or fragment is not conjugated with a detectable moiety.

220. The therapeutic composition of claim 219, wherein said genetically-engineered antibody of (2)(a) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, or said fragment of (2)(b) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that binds beta-amyloid and disaggregates an aggregate of human β-amyloid and said monoclonal antibody is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of human beta-amyloid.

221. The therapeutic composition of claim 219 or 220, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

222. A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a human monoclonal antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or

(b) a fragment of the human monoclonal antibody of (a) that binds beta-amyloid and disaggregates an aggregate of β-amyloid,

wherein said human monoclonal antibody is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid.

223. The therapeutic composition of claim 222, wherein said human monoclonal antibody of (2)(a) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, or said fragment of (2)(b) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, and wherein said human monoclonal antibody of (a) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of human beta-amyloid.

224. A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or (b) a fragment of the genetically-engineered antibody of (a), which fragment binds beta-amyloid and disaggregates an aggregate of β-amyloid, said method comprising:

selecting a monoclonal antibody that

(i) binds beta-amyloid and disaggregates an aggregate of β-amyloid, and

(ii) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or a fragment of a genetically engineered antibody, which fragment binds beta-amyloid and disaggregates an aggregate of β-amyloid; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

225. A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or

(b) a fragment of the genetically-engineered antibody of (a) that binds beta-amyloid and disaggregates an aggregate of β-amyloid,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) binds beta-amyloid and disaggregates an aggregate of β-amyloid and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid, and

wherein said antibody or fragment is not conjugated with a detectable moiety.

226. The therapeutic composition of claim 225, wherein said genetically-engineered antibody of (2)(a) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, or said fragment of (2)(b) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that binds beta-amyloid and disaggregates an aggregate of human β-amyloid and said monoclonal antibody recognizes an epitope within residues 1-28 of human beta-amyloid.

227. The therapeutic composition of claim 225 or 226, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

228. A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or (b) a fragment of the genetically-engineered antibody of (a), which

fragment binds beta-amyloid and disaggregates an aggregate of β-amyloid, said method comprising:

selecting a monoclonal antibody that

(i) binds beta-amyloid and disaggregates an aggregate of β-amyloid, and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or a fragment of a genetically engineered antibody, which fragment binds beta-amyloid and disaggregates an aggregate of β-amyloid; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

EVIDENCE APPENDIX

1. Bacskai et al., "Imaging of Amyloid-β Deposits in Brains of Living Mice Permits Direct Observation of Clearance of Plaques with Immunotherapy", *Nature Medicine*, 7:369-372 (2001)

2. Hanan et al., "Inhibitory Effect of Monoclonal Antibodies on Alzheimer's β-Amyloid Peptide Aggregation", *Amyloid: Int. J. Exp. Clin. Invest.*, 3:130-133 (1996).

3. Bard et al., "Peripherally Administered Antibodies Against Amyloid β-Peptide Enter the Central Nervous System and Reduce Pathology in a Mouse Model of Alzheimer Disease", *Nature Medicine*, 6:916-919 (2000).

4. Johnson-Wood et al., "Amyloid Precursor Protein Processing and Aβ42 Deposition in a Transgenic Mouse Model of Alzheimer Disease", *Proc. Natl. Acad. Sci. USA*, 94:1550-1555 (1997).

5. Bard et al., "Epitope and Isotype Specificities of Antibodies to β-Amyloid Peptide for Protection Against Alzheimer's Disease-like Neuropathology", *Proc. Natl. Acad. Sci. USA*, 100:2023-2028 (2003).

6. Solomon et al., "Monoclonal Antibodies Inhibit in vitro Fibrillar Aggregation of the Alzheimer β-Amyloid Peptide", *Proc. Natl. Acad. Sci. USA*, 93:452-455 (1996).

7. Solomon et al., "Disaggregation of Alzheimer β-Amyloid by Site-Directed mAb", *Proc. Natl. Acad. Sci. USA*, 94:4109-4112 (1997).

8. Solomon et al., "The Amino Terminus of the β-Amyloid Peptide Contains an Essential Epitope for Maintaining its Solubility", in Progress in Alzheimer's and Parkinson's Diseases, Fisher et al., ed., Plenum Press, New York, 205-211 (1998).

9. DeMattos et al., "Peripheral Anti-Aβ Antibody Alters CNS and Plasma Aβ Clearance and Decreases Brain Aβ Burden in a Mouse Model of Alzheimer's Disease", *Proc. Natl. Acad. Sci. USA*, 98:88-50-8855 (2001).

10. Frenkel et al., "High Affinity Binding of Monoclonal Antibodies to the Sequential Epitope EFRH of β-Amyloid Peptide is Essential for Modulation of Fibrillar Aggregation", *Journal of Neuroimmunology*, 95:136-142 (1999).

11. Schenk., US 6,761,888 - Table 16 (col 63).

RELATED PROCEEDINGS APPENDIX

None.